UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE GENERAL CAUSATION OPINION OF PLAINTIFFS' EXPERT STEPHEN LAGANA, M.D.

MAZIE SLATER KATZ & FREEMAN, LLC
103 Eisenhower Parkway, Suite 207
Roseland, New Jersey 07068
(973) 228-9898
Attorneys for Plaintiffs

On the Brief:
Adam M. Slater, Esq.
Christopher Geddis, Esq.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Rules

Other Authority

PRELIMINARY STATEMENT

This shotgun *Daubert* motion is set against the backdrop of a well-established scientific and regulatory consensus that NDMA and NDEA are probable human carcinogens. Dr. Lagana's opinions fall directly in line with the weight of authority, grounded upon the scientific evidence across animal studies, mechanistic studies, human dietary studies, occupational studies, and the few human epidemiology studies evaluating health claims data of users of valsartan. Every category of evidence and the most prominent studies were all considered. Failing to contend with the fact that Dr. Lagana took all of this into account and that his opinions are directly in line with this body of peer-reviewed scientific literature, Defendants instead resort to mischaracterizations, partial citations, and hyper-technical but inconsequential attacks on Dr. Lagana's background and the application of his methodology.

In essence, the defense previews a cross-examination that would go to the weight of the conclusions reached, at most, but in no way would establish that Dr. Lagana lacked the necessary qualifications, or that he failed to apply an acceptable scientific methodology. In fact, Dr. Lagana testified to applying the well-accepted weight of evidence and Bradford Hill methodologies.

Dr. Lagana's qualifications are more than sufficient, and his methodology is sound; thus, the motion should be denied.

STATEMENT OF FACTS

NDMA and NDEA are probable human carcinogens, and should be treated "for all practical purposes" as causing cancer in humans. (Internal Agency for Research on Cancer, *Some N-Nitroso Compounds*, in *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.*, 107, 152 (Lyon, Fr.

1978), Ex. 1).[1,2] The World Health Organization's 2002 peer-reviewed publication addressing the carcinogenicity of NDMA concluded:

> DNA adducts (in particular, O6-methylguanine) formed by the methyldiazonium ion generated during metabolism likely play a critical role in NDMA carcinogenicity. Observed variations in carcinogenicity among species and strains correlate well with variations in activity of O6-methylguanine DNA-methyltransferase. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O6-methylguanine has been detected in human tissues exposed to NDMA.
>
> **Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to human**s.

(Liteplo & Meek, *Concise International Chemical Assessment Document 38 – N-Nitrosodimethylamine*, at 23 (2002); Ex. 19, emphasis added (cited in Lagana Report, at 5-6, 12-13, 22)).

---

[1] Unless otherwise noted, all exhibits are from Adam M. Slater's Certification in Support of Plaintiffs' Opposition to Defendants' Motion to Exclude the General Causation Opinion of Stephen Lagana, M.D.

[2] The FDA has concluded that "NDMA and NDEA are probable human carcinogens and should not be present in drug products," the EPA considers NDMA and NDEA to be probable human carcinogens, and USP has said, "their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens." (FDA, *FDA presents interim limits of nitrosamines in currently marketed ARBs* (Dec. 19, 2018), https://tinyurl.com/4rkpdf5h, Ex. 2; EPA, *N-Nitrosodimethylamine*, https://tinyurl.com/9krh69u9, Ex. 3; EPA, *N-Nitrosodiethylamine*, https://tinyurl.com/48y7nejw, Ex. 4; USP, Summary, Highlights and Timeline of General Chapter <1469> Nitrosamine Impurities (July 20, 2018), Ex. 5). Multiple defense experts also conceded that NDMA and NDEA are probable human carcinogens, as discussed in Plaintiffs' affirmative Daubert briefs. (*See, i.e.*, Pls.' Br. in Supp. of *Daubert* Mot. to Preclude Ops. of Def. Expert Janice K. Britt, p. 4; Pls.' Br. in Supp. of *Daubert* Mot. to Preclude Ops. of Def. Expert Daniel Catenacci, p. 7).

The mechanistic evidence in the peer-reviewed scientific literature is quite strong, for example, a human dietary study stated in part:

> **The results of several in vitro studies suggest that N-nitroso compounds exhibit similar biological activity in human and animal tissues. Montesano and Magee (1974) have shown that liver slices from various species including humans can metabolise NDMA** (Table 3).

(Tricker & Preussmann, *Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential*, MUTATION RESEARCH 259, 277-89 (1991), Ex. 6; *see also* White, *Understanding and Preventing (N-Nitrosodimethylamine) NDMA Contamination of Medications*, THE ANNALS OF PHARMACOTHERAPY 54, 611-4 (2020) (stating: "NDMA, like other nitrosamine contaminants, activates ras oncogenes, and NDMA metabolism by CYP2E1 creates methyldiazonium, a known mutation inducer via methylation. As such, NDMA is suspected to cause both localized and systemic carcinogenic effects."), Ex. 7).

Defendants and their 30(b)(6) witnesses have also conceded that these substances are probable human carcinogens, and that the NDMA and NDEA in the contaminated valsartan increased the risk of cancer for those taking the pills. For example, ZHP subsidiaries Prinston and Solco, which were responsible for marketing and distribution of ZHP finished dose in the United States, unequivocally stated in announcing the recall, "[redacted]."[3] Likewise, the ZHP Deviation Investigation Report for the TEA process, which was submitted to the FDA, stated: "[redacted]." (PRINSTONO0075850, Ex. 9), emphasis added. ZHP 30(b)(6) witness Min Li, Ph.D.

[3] (SOLCO00024226, Ex. 8).

conceded that NDMA and NDEA are "probable human carcinogens,"[4] and that this [redacted] ."[5] Similarly, Hetero's 30(b)(6) witness conceded that NDMA is a probable human carcinogen which increased the risk of cancer for the people who took those contaminated pills. (B.V. Ramarao 4/29/21 Dep. Tr. 259:20-268:4, Ex. 11; 4/30/21 Dep. Tr., 342:14-343:19, 377:5-20, Ex. 12 (cited in Lagana Report at 31)).

A. Dr. Lagana's Background and Qualifications.

Dr. Lagana is an Associate Professor of Pathology and Cell Biology at Columbia University/NY Presbyterian Hospital, with a sub-specialty fellowship in gastrointestinal (GI), liver, and surgical pathology at Columbia. Dr. Lagana has both clinical and academic responsibilities, performs original research, and has published numerous articles in the peer-reviewed literature. He is a peer reviewer for multiple medical journals, including Modern Pathology, Archives of Pathology and Laboratory Medicine, BMC Cancer, Oncotarget, and the Journal of Clinical Pathology. He is Co-director of Molecular Testing in Surgical Pathology at Columbia, and a member of the Columbia Oncology Operations Council. (Dr. Lagana Report, ECF 1718-4, at 1-3, CV at Ex. 1 to Report, Ex. 13 hereto).

Dr. Lagana testified that a number of his peer-reviewed articles address causation of cancer, and he explained in detail how he takes general causation into account both in his clinical work and his research and peer-reviewed publications. (Dr. Lagana Dep. Tr., 110:4-122:9, ECF 1718-5). Commenting on one of his articles, he pointed out: "For example, saying that we looked at

[4] (Min Li 4/22/21 Dep. Tr., 696:3-697:10, Ex. 10).
[5] (*Id.* at 647:9-648:5 (cited in Dr. Lagana Report at 30-31)).

4,000 patients and we found X percent had this mutation and we think this may be driving their cancer, that is pathobiology of cancer, that's causation of cancer. And presumably, those are not the only patients on earth with that situation." (*Id.* at 116:13-117:9). He rejected defense counsel's effort to get him to say that he is not an expert regarding cancer, "You can't really separate pathology and cancer this way. Cancer is a major concern of pathology…knowing the etiology of cancers and what causes cancer, what's the pathobiology of cancer from both the population level down to a molecular level is definitely part and parcel of what a pathologist needs to know."[6] (*Id.* at 185:8-186:19). Dr. Lagana has peer-reviewed publications that have dealt squarely with issues of causation in human disease, including cancer. For example, he was a contributing author on a peer-reviewed study published in the journal of the American Heart Association, CIRCULATION, which identified a novel genetic mutation which caused sudden cardiac death in certain families (with a condition known as Brugada syndrome). (London, Michalec, Mehdi, Zhu, Kerchner,

---

[6] Peer-reviewed literature and the field of pathology agree with Dr. Lagana's understanding of pathology:

> Pathology (from the Greek word pathología, meaning the study of suffering) refers to the specialty of medical science concerned with the cause, development, structural/functional changes, and natural history associated with diseases. …. Pathologists diagnose disease by generating a differential diagnosis, then finding the best fit for the clinical presentation, the radiographic appearance, and the pathologic (both clinical lab and morphologic) findings. …. The mental construct of etiology (cause), pathogenesis (progression), natural history (clinical outcome), and response to therapy is the standard approach for pathologists thinking about a disease.

(*See* Funkhauser, *Pathology: The Clinical Description of Human Disease*, in *Molecular Pathology*, p. 197-207, 197, 203 (Elsevier, Inc. 2009), Ex. 14). The Medical University of the Americas provides the following definition of a pathologist: "**Medical pathology is the study of the *causes* and effects of injury and disease…. Identify the *etiology*, pathogenesis, morphological change, and clinical significance of diseases.**" (*What Do Pathologists Do?* (Sept. 14, 2021), https://tinyurl.com/22ma8bd5).

Sanyal, Viswanathan, Pfahnl, Shang, Madhusudanan, Baty, Lagana, Aleong, Gutmann, Ackerman, McNamara, Weiss, Dudley, *Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias*, CIRCULATION. 116, 2260-8 (Nov. 2007), Ex. 15). Specifically, the article concluded: **"GPD1-L is a novel gene that may affect trafficking of the cardiac Na+ channel to the cell surface. A GPD1-L mutation decreases SCN5A surface membrane expression, reduces inward Na+ current, and causes Brugada syndrome."** (*Id.*). Dr. Lagana co-authored a paper demonstrating that a common oral bacterium contributes to colorectal cancer in some instances. (Rubinstein, Baik, Lagana, Han, Raab, Sahoo, Dalerba, Wang, Han, *Fusobacterium nucleatum promotes colorectal cancer by inducing Wnt/β-catenin modulator Annexin A1*, EMBO REP. 20 (Apr. 2019), Ex. 16). Specifically, the anaerobe Fusobacterium nucleatum contributes to colorectal cancer by activating Wnt/beta-catenin signaling, which is a commonly activated pathway in colorectal cancer. (*Id.*). A recent study Dr. Lagana co-authored with physicians at the Mayo Clinic sought to identify what genetic changes caused certain individuals to develop an unusual type of liver cancer. (Van Treeck, Mounajjed, Moreira, Orujov, Allende, Bellizzi, Lagana, Davila, Jessen, Graham, *Transcriptomic and Proteomic Analysis of Steatohepatitic Hepatocellular Carcinoma Reveals Novel Distinct Biologic Features*, AM. J. CLIN. PATHOL. 155, 87-96 (Jan. 2021), Ex. 17). The study found: "**Pathway analysis comparing tumor-nonneoplastic pairs revealed significant upregulation of the hedgehog pathway based on GLI1 overexpression and significant downregulation of carnitine palmitoyltransferase 2 transcript. Glutamine synthetase transcript was significantly upregulated, and fatty acid binding protein 1 transcript was significantly downregulated and immunohistochemically confirmed, indicating steatohepatitic hepatocellular carcinoma tumor cells display a zone 3 phenotype.**" (*Id.*). Dr. Lagana also

demonstrated his deep knowledge of the mechanisms that cause cancer when he was questioned at his deposition, for example when questioned as to whether he could provide any examples of cancers caused by one mutation in a cell, "CK mutations in the gastrointestinal stromal tumors are a well-known example; the BRAF V600 mutation in melanoma, in some colorectal cancers. . . BRCA1, PROP1 mutation, breast ovarian cancers. This is not rare where one mutation drives a cancer." (Dr. Lagana Dep. Tr., 183:11-185:7).

B. Dr. Lagana Did Not Simply Confirm a Favored Opinion.

A central defense mischaracterization of Dr. Lagana's opinion is the argument that Dr. Lagana assumed causation of cancers by NDMA and NDEA before he performed his analysis—thus not starting with the null hypothesis. Contrary to that argument, Dr. Lagana followed the proper scientific approach: "I considered my role to look through the medical and scientific literature to form an opinion and then to express an opinion." (*Id.* at 165:16-25). When asked to confirm that he didn't just make assumptions: "With respect to the key issues, I would look at the literature and statements from regulatory agencies, like WHO, IARC, FDA, as I did and come to an opinion, yeah." (*Id.* at 175:24-176:10).

Defendants' argument is deliberately misleading, based on an isolated introductory background statement from Dr. Lagana's report regarding the real-world application of a differential diagnosis to determining the cause of an individual's cancer, "Therefore, for any patient who develops cancer, and is known to have a significant exposure to a probable human carcinogen…in a patient with cancer…" (Dr. Lagana Report at 11-12). In his deposition, Dr. Lagana illustrated this by reference to exposures to cigarette smoking and HPV. (Dr. Lagana Dep. Tr. 177:12-178:11). Dr. Lagana left no doubt that he proceeded properly, and that the defense argument is misleading: "I think it's unfair to characterize the whole report based on that statement.

…. So in that statement, it's talking about a particular patient. I'm not talking about a general approach or methodology to reviewing scientific literature. .... That's dealing with looking at a particular patient. It's not dealing with taking the literature as a whole." (*Id.* at 297:17-299:19).

Examining the report shows what Dr. Lagana actually did, as opposed to what the Defendants say he did, based on a deliberately incomplete and misleading argument. Having mentioned the background significance of identifying exposure to a probable human carcinogen in the evaluation of a specific patient's cancer, Dr. Lagana's report immediately transitioned to the scientific consensus that NDMA is a probable human carcinogen, and "highly likely to be carcinogenic to humans," and then to his evaluation of the literature on the general causation question: "Having provided a framework through which to consider the potential etiologic role of a specific carcinogen in a particular patient's cancer.... I will now describe evidence which I found informative." The next sentence demonstrates that Dr. Lagana rooted his analysis of general causation in peer-reviewed literature: "Several studies provide convincing evidence of an association between dietary NDMA and colorectal cancer…" (Dr. Lagana Report at 12). Dr. Lagana then discussed the dietary literature.[7]

The discussion of the first article in his evaluation of the dietary literature demonstrates that Dr. Lagana's treatment of the literature was thorough, as he: (1) summarized key findings including a 46% increased risk for rectal cancer, (2) pointed out that this helps to establish Bradford Hill criteria one, "strength of association," (3) explained why this "makes sense mechanistically, since the GI tract has rapid cell turnover…and as discussed previously, alkylating agents are most

[7] Defendants falsely suggest (Def. Br. 16) that Plaintiffs' experts Dr. Etminan and Dr. Hecht rejected the dietary literature as unreliable. Both of those Plaintiffs' experts relied on the dietary literature in part. Their agreement during their depositions that one can come up with criticisms of studies is hardly groundbreaking news, since that is probably true of virtually every study at some level, and certainly does not serve to exclude an entire category of relevant scientific data.

deleterious to dividing cells," (4) noted that this is the part of the colon with the least water content and thus, "the part of the large bowel with the most concentration of the carcinogen," and (5) pointed out the highly relevant fact that the cancer risk increased significantly at an NDMA exposure level very close to the FDA limits, "This highest exposure group with their markedly increased cancer risk was determined to be consuming approximately 126 ng/d of NDMA." (Dr. Lagana Report at 12-13). The defense's misleading arguments cannot wipe away the appropriate scientific analysis Dr. Lagana conducted.[8]

LEGAL ARGUMENT

I.

DR. LAGANA IS WELL QUALIFIED

The Third Circuit, "made clear in *Paoli II,* an expert's level of expertise may affect the reliability of the expert's opinion." *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000) (quoting *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 741 (3d Cir. 1994)). Dr. Lagana's extensive qualifications, set forth in detail above and discussed herein, strongly support a finding of reliability.

Defendants take broad shots at Dr. Lagana. In addition to falsely suggesting that Dr. Lagana does not have the qualifications to understand and opine regarding cancer, addressed above, they ignore Dr. Lagana's background in the use and understanding of epidemiology and

[8] The defense's misleading suggestion that Dr. Lagana's approach was to just apply his common sense to form his opinions is just as disingenuous. As part of a back and forth with defense counsel that was not centered on his methodology, Dr. Lagana remarked, "if I want to know if jumping out of the ninth floor is harmful, should I start with the null hypothesis or could I use a little bit of common sense?" (Dr. Lagana Dep. Tr., 296:2-12). Here, Dr. Lagana reviewed all categories of relevant evidence, and ultimately agreed with the scientific consensus that NDMA and NDEA can cause cancer in humans. On the other hand, as set forth in Plaintiffs' Daubert briefs, Defendants' experts ignored much of the relevant literature and the scientific consensus.

misrepresent the basis for his opinions in an effort to portray him as a non-epidemiologist posing as an epidemiologist. However, his background is sufficient to allow him to incorporate epidemiological literature into his analysis: "I learned epidemiology in medical school. I am aware of epidemiological concepts. And I've worked with and published with epidemiologists." (Dr. Lagana Dep. Tr., 122:10-19; *see* Lagana, Parwani, & Nichols, *Cardiac sarcoidosis: a pathology-focused review*, ARCH. PATHOL. LAB. MED. 134, 1039-46 (Jul. 2010) (**a peer-reviewed article by Dr. Lagana containing an entire section on epidemiology**), Ex. 18). This background and knowledge is more than sufficient. *In re Johnson & Johnson Talcum Powder Prods. Liab. Litig.*, 509 F. Supp. 3d 116, 192 n.52, 197 (D.N.J. 2020) (stating, **"[M]edical doctors do not need to be epidemiologists in order to testify regarding epidemiological studies"** (quoting *In re Mirena IUD Prods. Liab. Litig.*, 169 F.Supp.3d 396, 426 (S.D.N.Y. 2016)); *Glynn v. Merck Sharp & Dohme Corp.*, No. 11-5304, 2013 WL 1558690, at *2 (D.N.J. Apr. 10, 2013) (admitting testimony of orthopedist over objections that he was not trained in epidemiology and lacked familiarity with epidemiological terms and concepts because the expert "does not have to possess a particular subspecialty—epidemiology—to testify as an expert") (Ex. 22); *see also In re Abilify (Apriprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1348 (N.D. Fla. 2018) (holding that the "fact that Dr. Glenmullen is not an epidemiologist does not disqualify him from testifying about epidemiological studies" (collecting cases)).

Defendants go even further in misrepresenting what Dr. Lagana did here, also stating, "Dr. Lagana has no specialized expertise in epidemiology, yet offers opinions exclusively based on his selective review of epidemiology literature." (Defs.' Br. 23). Of course, as set forth above and throughout the brief, epidemiology literature was not the exclusive basis for his opinions, but rather

only one category of scientific evidence considered by Dr. Lagana.[9]

The cases relied on by Defendants to support their argument here are all off point. *Aloe Coal v. Clark Equipment Co.* addressed an expert (a sales representative) with essentially no relevant background experience to testify regarding the cause of a construction equipment fire. 816 F.2d 110, 114 (3d Cir. 1987). *Higgins v. Koch Development Corp.* precluded a treating doctor from opining on specific causation after the plaintiff failed to provide the required disclosures (including "a summary of the facts and opinions to which the witness is expected to testify") or explain how the expert was qualified or applied a reliable methodology in assessing the plaintiff's injuries. 794 F.3d 697, 704 (7th Cir. 2015). In *In re Viagra Products Liability Litigation*, the Court precluded an epidemiologist with no medical degree from offering a specific causation opinion for a patient's vision loss. 658 F. Supp. 2d 950, 960 (D. Minn. 2009). There is nothing in those cases that speaks to the record here.

II.

DR. LAGANA'S METHODOLOGY IS RELIABLE

The admissibility of expert testimony is determined pursuant to Rule 702, which incorporates the *Daubert* standard.

> In determining reliability, a court may look to several non-exhaustive factors, including:
>
> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the

[9] Similarly, when challenged on the biology of cancer, he testified: "I am an expert on pathobiology. And so to acquire that expertise, I do stay abreast of the medical literature and scientific literature. And I do read it as part of my routine practice." (Dr. Lagana Dep. Tr., 173:4-25).

> qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Geiss v. Target Corp., No. 09–2208 (RBK/KMW), 2013 WL 4675377, at *4 (D.N.J. 2013) (quoting *Elcock v. Kmart Corp.*, 233 F.3d 734, 745-47 (3d Cir. 2000) (Ex. 20)). In applying the *Daubert* standards, Courts are cognizant that, "Rule 702 has a liberal policy of admissibility." *Geiss*, 2013 WL 4675377 at *4 (citing *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008), other citations omitted.

Dr. Lagana applied both the weight of evidence methodology and the Bradford Hill viewpoints/criteria. Both are well-accepted methodologies in the Third Circuit: "[W]e accept that the Bradford-Hill and weight of evidence analyses are generally reliable." *In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d 787, 795-797 (3d Cir. 2017) (citing *Milward v. Acuity Specialty Prods. Grp.*, 639 F.3d 11, 17 (1st Cir. 2011) (recognizing the role of judgment, and that "no one type of evidence must be present before causality may be inferred." at 17-18)). Dr. Lagana's analysis was more than sufficient from a methodological standpoint, as Defendants cannot nearly meet the standard for exclusion: "A court should not, however, usurp the role of the fact-finder; instead, an expert should only be excluded if the flaw is large enough that the expert lacks the 'good grounds' for his or her conclusions." *Id.* at 792-793.

Courts in the Third Circuit routinely rely on the Federal Judicial Center's Reference Manual on Scientific Evidence (3d ed. 2011)[10] for guidance in evaluating the reliability of an expert's methodology for purposes of ruling on *Daubert* motions. *See, e.g.*, *In re TMI Litig.*, 193 F.3d 613, 707–08 (3d Cir. 1999), *as amended*, 199 F.3d 158 (3d Cir. 2000); *Talcum*, 509 F. Supp. 3d at 130 n.7, 133 n.9, 136, 160 n.34; *see also Reed v. Binder*, 165 F.R.D. 424, 429 n. 9 (D.N.J.

[10] A free PDF of the manual is available at the following link: https://tinyurl.com/2bu96z7f.

1996) (Kugler, J.) (relying on the Manual outside of the *Daubert* context). The *Reference Manual* states, "**Multiple avenues of deductive reasoning based on scientific data lead to acceptance of causation in any field, particularly in toxicology.** However, the basis for this deductive reasoning is also one of the most difficult aspects of causation to describe quantitatively. **If animal studies, pharmacological research on mechanisms of toxicity, in vitro tissue studies, and epidemiological research all document toxic effects of exposure to a compound, an expert's opinion about causation in a particular case is much more likely to be true.**" P. 674. The *Reference Manual* then drops a footnote and quotes *Marsee v. United States Tobacco Co.*, 639 F. Supp. 466, 469–70 (W.D. Okla. 1986), stating, "There was no dispute that both nitrosamines and polonium-210 are present in defendant's snuff products. Further, defendant conceded that animal studies have accurately and consistently demonstrated that these substances cause cancer in test animals**. Finally, the Court found evidence based on experiments with animals particularly valuable and important in this litigation since such experiments with humans are impossible. Under all these circumstances, the Court found this evidence probative on the issue of causation.**" *Id.* at 674-75. This applies directly here.

There is also legal authority for acceptance of an expert's opinions on cancer causation in the absence of human epidemiology. *In re Paoli Railroad Yard PCB Litigation* is a Third Circuit case in which the District Court's grant of summary judgment on claims for medical monitoring was reversed on appeal holding:

> Here, where the EPA has relied on animal studies to conclude that PCBs are a probable human carcinogen, where there is reason to think that animal studies are particularly valuable because animals react similarly to humans with respect to the chemical in question, and where the epidemiological data is inconclusive and some of it supports a finding of causation, we think that the district court abused its discretion in excluding the animal studies. Certainly, the evidence meets the relevance requirements of Rule 402 and we

> think, after taking a hard look, that it also meets the reliability requirement of Rules 702, 703 and 403.

35 F. 3d 717, 781 (3d Cir. 1994). The Third Circuit also noted:

> …"PCBs are not only considered as 'potential' human carcinogens, but as probable human carcinogens (Class B) by the Agency on the basis of conclusive experiments in test animals." In fact, EPA thinks that PCBs have the same carcinogenic potency as vinyl chloride, which is one of only 14 chemicals that EPA has indicated have been proven to be carcinogenic by epidemiological studies. **The "more probable than not" standard employed by EPA is the same standard that is employed in civil litigation.**

Id. at 780 (emphasis added). This analysis applies to the facts of this case as well.

Applying the weight of evidence methodology in line with the above authority, Dr. Lagana factored in every category of relevant scientific data presented in the peer-reviewed literature, including the animal studies, human dietary studies, mechanistic studies, occupational literature, and human epidemiology studies involving users of valsartan. (Dr. Lagana Report).[11] In *Zoloft,* the Court observed with regard to the application of the weight of evidence in that litigation that "the particular combination of evidence considered and weighed here has not been subjected to peer review." *Zoloft*, 858 F.3d at 797. That contrasts with this case, where the literature relied on has been peer-reviewed, including by the WHO, and across peer-reviewed literature—every study

[11] One of the most egregious—and inconsistent—misrepresentations by the defense is the repeated suggestion that Dr. Lagana's opinions are based solely on a review of epidemiology literature (vs. the contradictory charge in other places that he focused primarily on the dietary and animal studies). One need only read Dr. Lagana's report to confirm that this attack is completely false. For example, he discusses the mechanistic studies: "Further, 2 mechanisms have been discussed by which NDMA causes mutation and cancer. Specifically, those were alkylating DNA, a process which targets dividing cells (e.g., GI tract, skin) and activation of RAS family oncogenes, a process known to be pivotal to the formation of lung, pancreas, gastrointestinal tract, skin, thyroid, blood, and uterus cancers." (Dr. Lagana Report at 22). And he considered studies on both sides of the coin. "So the big question was not answered on the basis of any two studies. The big question was answered on the basis of pretty much everything that I've referenced here…including the negative studies." (Dr. Lagana Dep. Tr., 309:19-310:8).

relied on by Dr. Lagana is peer-reviewed.[12] The WHO's peer-reviewed weight of evidence methodology in addressing this question is mirrored by Dr. Lagana's weight of evidence approach. Dr. Lagana also applied the Bradford-Hill viewpoints/criteria in evaluating the question. This is more than sufficient. (*See* Dr. Lagana Report at 13, 14, 17, 22, 29-30, 33; Dr. Lagana Dep. Tr., 48:2-10, 49:12-13, 21-22; 176:6-10; 201:11-202:7; 272:17-273:4; 289:25-290:1; 290:8-13; 301:21-2; 309:24-310:8; 351:11-16; 362-19-363:11; 366:19-367:23; 376:9-377:3).

Dr. Lagana's opinions are based squarely upon and within a large body of peer-reviewed literature, and he is well-qualified; thus, the opinions easily satisfy these criteria (unlike the defense experts who sought to evade the peer-reviewed scientific consensus that NDMA and NDEA are probable human carcinogens by ignoring entire categories of directly relevant scientific literature). In the *Xarelto* litigation, a series of *Daubert* motions were summarily denied, with the Court succinctly opining that the plaintiffs' experts applied the proper methodology, and relied on peer-reviewed literature—as did Dr. Lagana—thus the balance of the defense's criticisms went to the weight of the opinions, not admissibility. *See In re Xarelto (Rivaroxaban) Prod. Liab. Litig.*, No. 2:14-MD-02592, 2017 WL 1352860 (E.D. La, Apr. 13, 2017) (Ex. 21). A similar conclusion is appropriate here.

Daubert requires that an expert, whether basing his opinions upon studies or personal experience, "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Elcock*, 233 F.3d at 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)). Dr. Lagana applied the methods and

[12] This stands in stark contrast to the defense experts, who almost uniformly failed to consider the cross-section of significant categories of scientific evidence directly relevant to the question of general causation, and ignored the damaging admissions by Defendants, which Plaintiffs have highlighted in the *Daubert* motions challenging defense experts' opinions.

knowledge he uses in his clinical and academic work at Columbia University, and offers an opinion that has been expressed in peer-reviewed scientific literature including those describing real-world experiments and studies, clearly satisfying these standards. When asked about his statement that he applied the methodology used in his work as a pathologist, he stated, "Yes. And I did. I consulted Peer Review literature which is what I do in clinical work. …. Part of my practice, though, is also to keep abreast of medical literature and need to produce medical literature. And so if someone were to ask me, as in this case, to look into the issue or issues around NDMA or NDEA, contamination of valsartan, you know, I wouldn't start looking at a glass slide. I would go to the PubMed. And the methodology I used was a research methodology, essentially, of looking at both statements from regulatory agencies and looking at original Peer Review medical research. And that's the approach I would take if I were writing a paper on a particular topic." (Dr. Lagana Dep. Tr., 99:13-21, 104:16-106:17). He further confirmed that consideration of general causation is part of his practice in response to repeated questioning attempting to get him to agree that his practice is limited to the review of slides: "No. I think that's mischaracterizing it, I think. Every pathologist – I'm an expert in pathobiology. So pathologists know about the causative factors of cancers and inflammatory illnesses. It's a major part of that. But it doesn't go in a report, usually. But not going in a report is different from not using that information or knowing that information." (*Id.* at 108:15-109:6).

In mischaracterizing Dr. Lagana's professional work, suggesting that all he does is hunch over a microscope reviewing specimens, they use a mischaracterization of his work in the *Benicar* litigation in this effort. When shown an excerpt from his *Benicar* report—which addressed the Olmesartan side effect of sprue-like enteropathy in the small intestine—Dr. Lagana pointed out that in that case, he was provided pathology specimens and evaluated them under the microscope,

in addition to his analysis of literature and, "We're talking about different things here. …. In this litigation, I haven't looked at any specific cases." (*Id.* at 102:8-103:19). That does not undercut the methodology applied here, in a different context, at all. The entire line of questioning regarding Dr. Lagana's work in Benicar proves nothing beneficial to the defense position.

Dr. Lagana's application of his methodology is fully in line with the peer-reviewed literature, as he clearly considered each relevant category of evidence—including countervailing studies in that body of literature—and explained how each fit into his overall analysis. (*See, i.e.*, Dr. Lagana Report at 13, 14, 17, 22, 29-30, 33). Dr. Lagana confirmed that he was "basing everything stated herein on the basis of the methodology I apply in my clinical and academic work, including reliance on and application of peer reviewed medical literature." (*Id.* at 3). Perhaps most important, he did not only analyze studies lining up with his opinion; he also addressed and factored in arguably negative and equivocal studies. For example, in the context of the dietary studies: "The studies, and in particular the dietary studies, are not uniform in their findings and conclusions. In general, given the comparatively lower (but still unacceptably dangerous) cancer risk from consuming lower levels of NDMA, these studies were likely underpowered. This is because smaller effects may require very large numbers of people in order to scientifically establish a causal relationship." (*Id.* at 19). He conducted a detailed analysis of the literature—pro and con—and concluded, "Considering this overall body of literature, it is likely that orally consumed NDMA is carcinogenic to humans...." (*Id.* at 12-21).[13] This approach more than suffices to establish "a scientific method of weighting that is used and explained." *Zoloft*, 858 F.3d at 796.

[13] Defendants suggest that Dr. Lagana did not consider the existence of negative dietary studies, citing to one study by Jakszyn which had findings published in 2011 and 2012 (Def. Br. 16-17), which is belied by the plain language of the report. He also did cite to and consider the results of at least two articles published by Jakszyn. (Dr. Lagana Dep. Tr., 30:6-18). There is certainly no requirement to evaluate every single article in the literature. *Talcum Powder*, 509 F.

Similarly, Dr. Lagana's application of Bradford Hill was clearly reliable.[14] His report analyzed and provided concrete examples of peer-reviewed literature establishing/satisfying each factor. His analysis was methodical, which is illustrated by his discussion of the difficulty in applying the 3rd criteria, specificity: "Bradford Hill's 3rd criteria, specificity, is more complex, as there are many factors which may generally contribute to carcinogenesis," an opinion he then discussed in the context of gastric cancer, as addressed in peer-reviewed studies cited in the report, and also pointed out that these factors, "are not intended to be rigidly applied, and nor is it necessary for each factor to be satisfied in order to establish a causal association." (Dr. Lagana Report at 29-30). Of course, Dr. Lagana is correct that all of the Bradford Hill factors need not be met. "One or more of the factors may be absent even where a causal relationship exists and…no factor is a sine qua non of causation." *Glynn v. Merck Sharp & Dohme Corp.*, Nos. 11–5304, 08–08, 2013 WL 1558690, at *3 (D.N.J. Apr. 10, 2013) (citing *Magistrini v. One Hour Martinizing Dry Cleaner*, 180 F. Supp. 2d 584, 593 n. 9 (D.N.J. 2002)) (Ex. 22); *see Milward*, 639 F.3d at 17 ("when a group from the National Cancer Institute was asked to rank the different types of evidence, it concluded that there should be no such hierarchy."). In *Glynn*, the *Daubert* motion to preclude the plaintiffs' expert on general causation was denied because, as here, the expert considered the Bradford Hill factors, and the criticisms went to the weight, not admissibility of the testimony, the Court concluding, "Defendant is free to address these issues on cross-examination…." 2013 WL 1558690, at *4.

Supp. 3d at 194 ("There is not, however, any requirement that an expert review every single study in the relevant body of literature.").

[14] Defendants' argument that Dr. Lagana's analysis of literature to address the general causation question here is somehow a methodological flaw in and of itself is not grounded in reality. If that were correct, only Dr. Hecht could testify in this case since he is the only expert for either side who actually has studied the carcinogenicity of NDMA and NDEA as a focused part of his scientific work.

The defense's strategy to obscure Dr. Lagana's methodology is so strained that they focus on Dr. Lagana's report in the *Benicar* litigation to try to undercut his methodology in this case, suggesting that he changed his approach from then to now. Putting aside the irrelevance of the argument, Dr. Lagana testified in his *Benicar* deposition that he took the Bradford Hill criteria into account in performing his analysis, and gave examples of how it was applied in that case. (Dr. Lagana *Benicar* Dep. Tr., 356:8-357:24, 403:17-405:5, 406:10-20, 407:2-10, Ex. 23). "Bradford-Hill criteria are used to assess whether an established association between two variables actually reflects a causal relationship. Because these criteria are so well established in epidemiological research, it appears that the experts often consider these factors without citation to Bradford–Hill." *In re Avandia Marketing, Sales Practices & Products Liab. Litigation*, No. 2007–MD–1871, 2011 WL 13576, at *3 (E.D. Pa., Jan. 4, 2011) (Ex. 24). What matters is that Dr. Lagana applied Bradford Hill, in addition to weight of evidence here.

A. Valsartan Human Epidemiology Studies.

Another illustration of the reliability of Dr. Lagana's methodology is his assessment of the human epidemiology evidence with regard to valsartan, which the defense inexplicably and confusingly suggests he ignored or failed to give adequate weight in his analysis, while stating elsewhere (Defs.' Br. 14-15) that this was the entire basis for his opinion. Aside from the inconsistency of the defense position, Defendants blatantly misrepresent that "Dr. Lagana's only reference to the Pottegård study is to say it 'suggest[s]' increased cancer risk in consumers of valsartan. Report, at 27." (Defs.' Br. 15). The discussion of Pottegård actually begins on page 24 of Dr. Lagana's report, with his acknowledgement that "[t]here were no statistically significant increases in cancer rates for the follow up period. However, non-significant trends towards increased cancer outcomes were observed. Specifically, there was a 46% increased risk of

colorectal cancer and an 80% increased risk of uterine cancer." Thus, he did exactly what the defense said he did not. Dr. Lagana also addressed what he perceived to be significant design flaws in the study potentially impacting the data and findings. (Dr. Lagana Report at 24-26). He also evaluated Gomm, and pointed out in part (contrary to Defendants' misrepresentation that Dr. Lagana did not note the overall findings in Gomm), "No effect was identified with respect to most cancers; however, there was a statistically significant increased risk of liver cancer. NDMA is metabolized in the liver, and liver tumors are common in animal models." (Dr. Lagana Report at 26).

Dr. Lagana testified at his deposition in more detail regarding the significance of the valsartan human epidemiology studies, weighting of the studies, and flaws in the studies—including short follow up periods, lack of certainty about the composition of the control groups in Pottegård and Gomm – thus likely including users of contaminated valsartan in the cohort of supposedly unexposed people, and the exclusion of patients with a prior cancer diagnosis in Pottegård. He stated, with regard to the non-statistically significant findings of increased risk for uterine and colorectal cancer in Pottegård, "those are the most common cancers in people who have deficient DNA cleanup machinery… patients with Lynch Syndrome," and, "I know the mechanism by which NDMA - - causes mutation in cells. And it's precisely the kind of thing that you would want the enzymes of Lynch Syndrome to face…" (Dr. Lagana Dep. Tr., 289:24-290:2, 299:20-300:16, 303:10-321:25). As set forth in his report and discussed in his deposition, **Dr. Lagana also evaluated a third peer-reviewed valsartan epidemiology study that was ignored by some defense experts completely**. (Al-Kindi & Oliveira, *Abrupt Increase in Reporting of Neoplasms Associated with Valsartan After Medication Recall*, CIRCULATION CARDIOVASCULAR

QUALITY AND OUTCOMES (July 2019), Ex. 25).[15] That study addressed adverse event reporting before and after the announcement of the valsartan contamination. As stated in his report, "What is particularly striking about this article is that the calculated risk of reporting a neoplasm as an adverse event was 70% higher for valsartan users compared to consumers of other angiotensin blockers even **before** the NDMA contamination was announced." (Dr. Lagana Report at 26-27 (citing Al-Kindi; Dr. Lagana Dep. Tr., 317:4-321:25)). If every relevant study must be addressed, why did Dr. Catenacci ignore this valsartan based human epidemiology study which supports general causation? (Ex. B to Pls.' *Daubert* Mot. to Preclude Ops. of Def. Expert Daniel Catenacci).

Of course, it is the method, not the conclusion, that is at issue, and there can be no reasonable criticism of a method that accounted for each of the valsartan epidemiology studies. Perhaps most important in responding to Defendants' over-emphasis on the lack of statistical significance seen for the increased risk for uterine and colorectal cancer in Pottegård (while they ignore the statistically significant finding for liver cancer in Gomm), statistical significance is not an outcome determinative talisman. "A causal connection may exist despite the lack of significant findings, due to issues such as random misclassification or insufficient power…. A standard based on replication of statistically significant findings obscures the essential issue: a causal connection. Given this, the requisite proof necessary to establish causation will vary greatly case by case." *In re Zoloft*, 858 F.3d at 794. In this respect, Defendants' comment that Dr. Lagana had an "apparent preference for dietary and animal studies to the human epidemiology data" (Defs.' Br. 16) is baffling since he considered all of that data, and the dietary and animal studies help to form the backbone of the scientific consensus for probable human carcinogenicity.

---

[15] This article was peer reviewed. (American Heart Association, *Circulation: Cardiovascular Quality & Outcomes* (stating, "Research Letters will be peer reviewed in a manner identical to original research articles"), https://tinyurl.com/vh4cn4tr, Ex. 26).

B. Dose and Duration of Exposure.

Another criticism by Defendants is the suggestion that Dr. Lagana disregarded dose and duration of exposure. However, Defendants completely overlook the law as applied in this District. In *Talcum*, the court wrote:

> Generally, "while precise information concerning the exposure necessary to cause specific harm to humans and exact details pertaining to the plaintiff's exposure are beneficial, **such evidence is not always available, or necessary, to demonstrate that a substance is toxic to humans given substantial exposure and need not invariably provide the basis for an expert's opinion on causation**." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 264 (4th Cir. 1999) (admitting expert testimony that exposure to talc caused sinus problems despite inability to determine threshold level of exposure necessary to cause plaintiff's injuries). Here, the Court acknowledges, as correctly pointed out by Defendants, that strong evidence of dose-response would tend to show a stronger causative relationship between talc use and ovarian cancer. However, based on epidemiological principles, a strong dose-response is not necessarily required for an expert to find a casual nexus. *See, e.g.*, *Ferguson v. Riverside Sch. Dist. No. 416*, No. 00-0097, 2002 WL 34355958, at *6 (E.D. Wash. Feb. 5, 2002) ("The Court determines that the lack of a model for determining causation based on a 'dose-response' relationship does not undermine the reliability of [the expert's] testimony."). Even so, the causation experts have pinpointed studies that demonstrate evidence of dose-response, i.e., meta-analyses, and adequately explained why the studies, themselves, are reliable. *See Green*, *supra* at 603.

509 F. Supp. 3d at 179. Dr. Lagana's opinions, which do take dose into account, satisfy this standard.[16]

First, with regard to dose, Dr. Lagana catalogued the NDMA and NDEA levels reported by the FDA and the generally higher levels disclosed by Defendants in discovery. (Dr. Lagana

[16] Moreover, Plaintiffs have experts who opine on the specifics of the dose-response relationship for NDMA and NDEA in this case to the extent it is necessary. However, Plaintiffs' experts do not need to each bear the burden of proving Plaintiffs' entire case individually. *See Talcum*, 509 F. Supp. 3d at 140-41 (allowing an expert to provide reliable opinions underlying general causation but not general causation itself).

Report at 7-11). Dr. Lagana stated in his report, "An old adage attributed to the ancient physician Paracelsus states that 'the dose makes the poison.' This axiom is worth keeping in mind throughout this discussion, since one must consider that any cancer risk detected via dietary studies is the 'tip of the iceberg' considering the dosages unwittingly ingested by users of contaminated products." (Dr. Lagana report at 4-5). He also compared the valsartan NDMA levels to the levels and comparative risks posed by eating pan-fried bacon and smoking cigarettes. (Dr. Lagana Report at 7). During his deposition, Dr. Lagana explained that "Understanding that there is no safe dosage and that any exposure is likely to increase risk of cancer, I would -- from that baseline, I would agree that bigger doses for longer duration are worse than smaller doses for shorter durations."[17] (Dr. Lagana Dep. Tr., 41:1-7). In response to questions concerning endogenous NDMA exposure, Dr. Lagana noted that "irrespective of what the baseline [of endogenous exposure] is, we still have the dietary studies, which fully weighted, you know, looking at them in their totality show an effect for doses of NDMA, you know, really getting into a little over 100 nanograms per day." (*Id.* at 232:10-16;*see* Song, Wu, & Guan, *Dietary Nitrates, Nitrites, and*

[17] Defendants also cite two cases that have rejected the "no threshold model," which argues that "when no safe-threshold of exposure to a carcinogen has been established, each and every exposure will increase the development of cancer." *Henricksen v. ConocoPhillips Co.*, 605 F.Supp.2d 1142, 1165-66 (E.D. Wa. 2009). However, Dr. Lagana did not rely on this assumption. Instead, he considered the peer-reviewed scientific literature and determined that NDMA and NDEA have shown to be carcinogenic at all levels due to their mechanism of action (namely, their ability to damage DNA and institute carcinogenesis). (*See, i.e.*, Tricker & Preussmann, *Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential*, Mutation Research 259, 277-89 (1991) (noting "the absence of a lower-no-effect threshold" for NDMA and NDEA based on scientific experiments), Ex. 6). **In fact, Lance Molnar, Ph.D., Mylan's Senior Director, Global Pharmacology and Toxicology, agreed in his deposition that nitrosamines are treated as non-threshold by "the EMA, FDA, ICH … regulatory bodies in general" and that "non-threshold effect would mean that a single molecule could be detrimental."** (Lance Molnar 5/07/2021 Dep. Tr., 125-2-6, 121:22-23, Ex. 31). Given the scientific support for the no threshold limit for NDMA and NDEA, the Court should reject Defendants' allegation that Dr. Lagana merely assumed any amount of a carcinogen is dangerous, so any amount of NDMA or NDEA must also be dangerous.

Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis, NUTRIENTS 7, 9872-95, at 9892-9893 (2015)). Thus, contrary to Defendants' misrepresentations, Dr. Lagana considered dose and duration and reasonably relied on peer-reviewed literature, including human dietary studies, to support his opinion.

C. The Hidajat Occupational Study.

Defendants also criticize Dr. Lagana's consideration of the Hidajat occupational study. First, addressing the route of exposure, Dr. Lagana relied on WHO and IARC for the conclusion that NDMA "induces benign and malignant tumors following administration via various routes, including digestion and inhalation in various organs and various species. It produces tumors of the liver, kidney and respiratory tract." (Dr. Lagana Dep. Tr. 375:8-22; *see also* WHO, *International Agency for Research on Cancer (IARC) - Summaries & Evaluations: N-NITROSODIMETHYLAMINE* (Mar. 27, 1998), https://tinyurl.com/yzbu8jxd (Ex. 27)). In trying to create this false issue, the defense fails to acknowledge that its own expert Dr. Catenacci conceded that inhaled NDMA is metabolized in the liver, same as orally consumed. (9/14/2021 Daniel Catenacci Dep. Tr. 305:15-24, Ex. 28). Second, Dr. Lagana did recognize and account for potential confounders in that study, including smoking, pointing out in his deposition that the authors "statistically modeled the potential for bias from smoking and concluded that it was not a significant confounding factor." (Dr. Lagana Dep. Tr., 352:3-354:15). Dr. Lagana also confirmed that he considered Hidajat in forming his opinion regarding latency. (Dr. Lagana Dep. Tr., 301:14-302:19, 350:24-351:16).

D. Endogenous NDMA Formation.

The defense also falsely suggests that Dr. Lagana did not account for the potential endogenous (inside the body) formation of NDMA, and has no opinions on that subject. On page

3 of his report, Dr. Lagana pointed out, "NDMA can be created within the body under the proper circumstances (e.g., after ingestion of nitrates and nitrites plus proteins)." (*See also* Dr. Lagana Report at 19-22 (discussing, in part, a dietary study and noting, "A fairly large European study found no increased risk of gastric cancer attributable to dietary NDMA, but did find increased risk for subjects who were high consumers of the building blocks of NDMA, who presumably synthesized high levels of NDMA internally (endogenous synthesis of NDMA)"). In an effort to create an issue, the defense takes a supposed concession in Dr. Lagana's deposition that he did not have an opinion as to what is more dangerous, endogenous or exogenous NDMA, completely out of context. Aside from the fact that this issue is not determinative of anything, the questioning that leads up to and shows the basis for his answer actually demonstrates that he has carefully considered, scientifically based opinions that explain the lack of significance to that question. He confirmed that he "certainly did" consider endogenous NDMA, read and considered the EMA statement that addressed endogenous NDMA formation, pointed out that this is a controversial area since "any study that has looked at endogenous production of NDMA is doing it by modeling and by inference," and discussed the variations in modeled levels including the "very high levels" modeled in the Hrudey study relied on by the defense, and other studies such as Choi which was cited in his report, "which show a much less, a much lower level of endogenous production." More to the point, he opined that there is not "a solid evidentiary basis to" compare endogenous and exogenous NDMA exposure, but pointed out that despite any assumed endogenous levels, the dietary studies still show a signal which supports a finding of causation by exogenous NDMA intake," and stated, "we still have the dietary studies, which fully weighted, you know, looking at them in their totality show an effect for doses of NDMA, you know, really getting into a little over 100 nanograms per day." (Dr. Lagana Dep. Tr. 219:19-233:14). Thus, Dr. Lagana considered

potential endogenous formation of NDMA and his opinion regarding endogenous formation of NDMA is logical and based on scientific analysis of peer-reviewed literature.[18]

E. Pre-Disposition to Cancer.

Another point of criticism is Dr. Lagana's opinion that one with a pre-disposition has a greater risk. This is presented by the defense as a bare opinion with no support. (Defs.' Br. 21). However, Dr. Lagana actually provided a detailed, reasoned explanation of the opinion, including consideration of mechanistic science, "Well, it's a scientific inference based on the fact that we know NDMA is an alkylating – or when it's metabolized, NDMA is an alkylating agent which causes methylguanine formation. Methylguanine is one of the most mutagenic nucleic acids known to man. So if you already have a problem predisposed to cancer, it's a perfectly reasonable scientific inference based on the mechanism of injury that those people would be at increased risk." (Dr. Lagana Dep. Tr., 364:21-366:12). When pressed to identify supportive literature Dr. Lagana did so, and provided further detailed mechanistic and genetic scientific support for the opinion. (Dr. Lagana Dep. Tr., 366:13-370:19). In fact, Dr. Lagana testified with regard to the Gomm study, which found a statistically significant increased risk of liver cancer, and also touched on this issue. That study states: "However, molecular mechanisms known for NDMA in the pathogenesis of liver cancer in experimental animals support an association with NDMA exposure in humans. It may be that NDMA exposure promotes cancer development in already existing, as yet undiagnosed early stages and thus hastens clinical manifestation." (Dr. Lagana Dep. Tr.,

[18] Once again glossing over the facts, the defense fails to mention that defense expert Dr. Catenacci was unable to offer an opinion on assumed levels of endogenous NDMA formation. (Daniel Catenacci 9/14/2021 Dep. Tr. 354:211-356:7; Pls.' Br. in Supp. of Their *Daubert* Mot. to Preclude Opinions of Def. Expert Daniel Catenacci, p. 10).

389:12-390:17). Thus, this proposition is supported by the human epidemiology studies the defense seeks to rely on most heavily.

F. Applicability of NDMA Literature to NDEA.

Defendants also criticize Dr. Lagana's opinion regarding the applicability of NDMA literature to NDEA (NDMA has been studied far more extensively). (Defs.' Br. 5). That criticism is based on a partial citation to language in Dr. Lagana's report. The full statement demonstrates that he grounded his opinion in peer-reviewed literature: "NDMA is the most widely studied, and is the one found in most abundance in valsartan. Therefore, I will focus most of the discussion on NDMA; however, NDEA has also been identified in valsartan, and according to researchers using both bacterial and experimental data, may be the most potent carcinogen of any known nitrosamine. Therefore, to the extent NDMA is discussed herein, the conclusions as to NDMA apply to NDEA as well, unless otherwise indicated." (Dr. Lagana Report at 5). This is no surprise, since the FDA feels the same way, having set a limit of 26.5 ng, as opposed to the NDMA limit of 96 ng. (FDA, *FDA presents interim limits of nitrosamines in currently marketed ARBs* (Dec. 19, 2018), https://tinyurl.com/4rkpdf5h, Ex. 2; Thresher, Foster, Ponting, Stalford, Tennant, & Thomas, *Are all nitrosamines concerning? A review of mutagenicity and carcinogenicity data*, REGULATORY TOXICOLOGY AND PHARMACOLOGY 116, 2 (2020) ("NDEA is the most potent nitrosamine for which carcinogenicity data is available") (cited in Dr. Lagana Report at 11) (Ex. 29). Moreover, as set forth above, the ZHP Deviation Investigation Report for the TEA process, which was submitted to the FDA, stated: "NDEA is considered as a probable human carcinogen based on projection from the animal studies." (PRINSTONO0075850, Ex. 9). This hardly fits the defense argument premised on exclusion of an opinion where "no association" is supported by the scientific literature, and "there is no basis to find a causal relationship." (Defs.' Br. 21-22). As

already noted, IARC states that NDEA is a probable human carcinogen and should be treated "for all practical purposes" as causing cancer in humans. (Internal Agency for Research on Cancer, Some N-Nitroso Compounds, in *IARC Monogr. Eval. Carcinog. Risk Chem. Hum.*, 107 (Lyon, Fr. 1978), Ex. 1).

G. Defendants' Arguments Go to the Weight of the Opinions, at Most.

The balance of Defendants' arguments, primarily based on mischaracterizations of Dr. Lagana's deposition testimony, go only to the conclusions reached and the weight to be given those conclusions, at most. This is not a permissible attack under *Daubert*. The focus of the reliability inquiry is on the expert's principles and methodology, not on his conclusions. *Glynn* at *2 (citing *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594-95 (1993)). The basis for this Court's finding that an expert should be precluded under *Daubert* in another case demonstrates by comparison why Dr. Lagana's opinions should not be impacted here. *Player v. Motiva Enterprises LLC*, No. Civ. 02–3216(RBK), 2006 WL 166452, at *6-7 (D.N.J. Jan. 20, 2006) (citations omitted) (Ex. 30). In *Player*, this Court found an expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, among other things. *Id.* at *7. The Court held: "His method is untestable and arbitrary, without a generally accepted, established, or peer-reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *8. None of those things can be said about Dr. Lagana's opinions.

CONCLUSION

For the foregoing reasons, Defendants' motion to preclude Dr. Lagana's opinions under *Daubert* should be denied. Dr. Lagana is well-qualified, and applied valid methodology, relying on peer-reviewed literature to form opinions fully consistent with the consensus in the peer-

reviewed literature. Whatever criticisms the defense may have may be directed to the weight to be accorded to the testimony, at most, and can be explored on cross-examination at trial.

Respectfully,

By: /s/ *Adam M. Slater*

ADAM M. SLATER
Mazie Slater Katz & Freeman, LLC
103 Eisenhower Parkway
Roseland, NJ 07068
973-228-9898
Fax: 973-228-0303
aslater@mazieslater.com

Dated: December 1, 2021

CERTIFICATE OF SERVICE

I hereby certify that on December 1, 2021, I electronically filed a partially redacted version of this brief and my supporting certification with the Clerk of the Court using CM/ECF system which will send notification of such filing to the CM/ECF participants registered to receive service in this MDL. In addition, I hereby certify that unredacted copies of foregoing document will be served contemporaneous to filing via email on the Court, Special Master, and the Defense Executive Committee at DECValsartan@btlaw.com.

MAZIE SLATER KATZ & FREEMAN, LLC
Attorneys for Plaintiffs

By: /s/ Adam M. Slater

Dated: December 1, 2021